Attorney Docket No: P-3639P1

Remarks

Status Of Claims

Claims 19-24, 26-55 and 61 - 63 are pending.

Claims 19-24, 26-55 and 61 - 63 stand rejected.

The Interview of August 20, 2003

In an interview with Examiner on August 20, 2003, both the written description and enablement rejections were discussed. The remarks that follow restate and elaborate on the arguments brought forth during the interview.

The Rejection Under The Written Description Requirement Of 35 U.S.C. §112, First Paragraph

Claims 19-24, 26-55 and 61 - 63[1] were rejected under the written description requirement of 35 U.S.C. §112, first paragraph (Paper 44, §5), for reasons of record, i.e., on the ground that the specification provides insufficient written description of the generic claim reciting the use of an inhibitor of cytokine secretion. Examiner, noting the large number of compounds that potentially could be encompassed by the term "inhibitor of cytokine secretion", suggested that the claimed genus has not been adequately described. Applicants traverse, in addition to the reasons of record, for the following two reasons, discussed more fully below:

1) The use of an inhibitor of cytokine secretion to allow intracellular cytokines to accumulate, thereby facilitating the detection of the intracellular cytokines was known at the time of the invention. The description need only describe in detail that which is new or not conventional (*Hybritech v. Monoclonal Antibodies*, 802 F.2d at 1384, 231 USPQ at 94 (Fed. Cir. 1986)).

[1] Applicants note that the present rejection encompasses all pending claims, whereas in the previous Office action (paper 40), only Claims 19-24, 26-33, 40, 43, 45, 47, 49-55, and 61-63 were rejected under the written description requirement of 35 USC §112, first paragraph. As no basis for extending the rejection has been stated, and as the present rejection would encompass even claim 39, drawn to the exemplified embodiment using Brefeldin-A as the inhibitor of cytokine secretion, Applicants assume that the current list of rejected claims is a typographical error. Furthermore, Applicants respectfully point out that if the rejection is applied to the previously non-rejected claims, this represents a new rejection which renders the finality of the rejection improper, and, in this case, Applicants request withdrawal of the finality. Applicants request clarification as to Examiner's intent.

2) The claims are drawn to a new use of known compounds (an inhibitor of cytokine secretion) and are *not* drawn to either novel compounds per se or to methods using novel compounds. In such a case, the applicant is not required to discover all the compounds from this class that would be useable in the methods (*In re Fuetterer*, 138 USPQ 217 (CCPA 1963)).

The use of an "inhibitor of cytokine secretion" to facilitate detection of intracellular cytokines was known in the art

The present claims are drawn to novel methods for detecting antigen-specific T cells by detecting intracellular cytokines following stimulation by contact with a nominal antigen. An inhibitor of cytokine secretion is used to allow intracellular cytokines to accumulate, thereby facilitating the detection of the intracellular cytokines.

The closest prior art of record describes methods for detecting T cells activated in a non-specific manner by detecting intracellular cytokines following stimulation by contact with a polyclonal stimulator. An inhibitor of cytokine secretion was used to allow intracellular cytokines to accumulate, thereby facilitating the detection of the intracellular cytokines. References of record that describe such methods, along with the particular inhibitor of cytokine secretion used, are provided in the table, below.

Inhibitor used	**Reference (all of record)**
Monensin	Jung et al., 1993, J. Immunol. Methods 159:197-207
Monensin	Elson et al., 1995, J. Immunol. 154(9):4294-4301
Monensin	Prussin et al., 1995, J. Immunol. Methods 188:117-128
Brefeldin-A	Picker et al., 1995, Blood 86:1408-1419
Brefeldin-A & monensin	Application Note 1: Detection of Intracellular Cytokines in Activated Lymphocytes, Becton Dickinson and Co.

Each of the references listed above describe methods in which an inhibitor of cytokine secretion is used to allow intracellular cytokines to accumulate in order to facilitate detection of the intracellular cytokines. Although the claimed methods are distinguished from these earlier methods both in specificity of activation and the subset of cells detected, the claimed methods include the use of an inhibitor of cytokine secretion for the same purpose, to allow intracellular cytokines to accumulate in order to

facilitate detection of the intracellular cytokines. This particular element of the present invention is old in the art and conventional to one of skilled in the art of detecting intracellular cytokines.

The description need only describe in detail that which is new or not conventional (*Hybritech v. Monoclonal Antibodies*, 802 F.2d at 1384, 231 USPQ at 94 (Fed. Cir. 1986)). The rejection is improper because it is based on an improper requirement to describe in great detail an element of the invention which is old in the art.

The claims are drawn to a new use of known compounds

Applicants further point out that the present claims are to a method that includes the use of an inhibitor of cytokine secretion, as was known in the art, not to the discovery of compounds useful as inhibitors of cytokine secretion. The Courts, in clarifying the written description requirement, have distinguished claims drawn to novel combinations or uses of known compounds from claims drawn to classes of new compounds per se or claims drawn to processes using those new compounds.

In *In re Fuetterer*, 138 USPQ 217 (CCPA 1963), claims drawn to a rubber stock composition useful in producing tire treads included a recitation of "an inorganic salt capable" of maintaining an homogeneous distribution of another component in the composition. The disclosure listed the function desired and four members of the class having that function. The claims had been rejected by the examiner as being overly broad ("'inorganic salt" reads on literally thousands of materials, many of which would not be operative for applicant's purpose'. Ibid at 220). The board agreed, noting that rejection was based on "the inordinate breadth of the claimed salts when it is not apparent from the disclosure of only four salts what other salts would be suitable to serve the function asserted and required by the claims" (Ibid at 220, 221). However, the Court overturned the rejection and found the written description requirement to be satisfied:

> Appellant's invention is the combination claimed and not the discovery that certain inorganic salts have colloid suspending properties. We see nothing in patent law which requires appellant to discover which of all those salts have such properties and which will function properly in his combination. The invention description clearly indicates that any inorganic salt which has such properties is usable in his combination. If others in the future discover what inorganic salts additional to those enumerated do have such properties, it is clear appellant will

> have no control over them per se, and equally clear his claims should not be so restricted that they can be avoided merely by using some inorganic salt not named by appellant in his disclosure.

Ibid at 138 USPQ at 223 (emphasis added). Applicants submit that the facts in the present case are analogous to those in *In re Fuetterer*.

As in *In re Fuetterer*, the present claims stand rejected as being overly broad in view of the large number of potential inhibitors of cytokine secretion. Analogously, the present claims are to a combination of steps (that includes the use of an inhibitor of cytokine secretion), not to the discovery of compounds that act as inhibitors of cytokine secretion. Following the reasoning of the Court, Applicants do not have to discover which of all the potential inhibitors of cytokine secretion will function properly in methods. Furthermore, if others in the future discover another suitable inhibitor of cytokine secretion, the present claims should not be so restricted that they can be avoided merely by using some inhibitor of cytokine secretion not described in the specification.

In summary, Applicants maintain that the description in the specification is sufficient to reasonably convey to one of skill in the art that Applicants conceived of methods using "an inhibitor of cytokine secretion". The element of the claimed invention that is the use of an inhibitor of cytokine secretion to achieve an accumulation of intracellular cytokines to facilitate detection was known at the time of Applicants' invention; the specification need not describe this known element in detail. Furthermore, the claims are to a combination of elements, one being the known use of an inhibitor of cytokine secretion, not to the discovery of compounds that act as inhibitors of cytokine secretion; again, the specification need not describe this known element in detail. For these reasons and in view of the case law discussed above, Applicants submit that the specification fully meets the written description requirement.

Applicants respectfully request reconsideration and withdrawal of the rejection of Claims 19-24, 26-55, and 61-63 under the written description requirement of 35 U.S.C. §112, first paragraph.

The Rejection Under The Enablement Requirement Of 35 U.S.C. §112, First Paragraph

Claims 19-24, 26-55, and 61-63 were rejected under 35 U.S.C. §112, first paragraph, for lack of enablement (Paper 44, §6), based on the grounds that a disclosed critical limitation is missing from the claims. In particular, Examiner cited language in Example 4 as teaching critical elements of the inventions that must be recited in the claims. Applicants traverse, in addition to the reasons of record, for the reasons set forth below.

Applicants submit that Example 4 describes a preferred mode of the invention and does not a teach of critical elements without which the invention would be wholly inoperative. Below, Applicants first discuss the applicable legal standard, then discuss Example 4 in view of the legal standard and, further, in view of art of record that provides factual evidence that disputes the contention that critical elements are omitted from the claims.

Legal Standard

A feature which is taught as critical in a specification and is not recited in the claims should result in a rejection of such claim under the enablement provision section of 35 U.S.C. 112. See *In re Mayhew*, 527 F.2d 1229, 1233, 188 USPQ 356, 358 (CCPA 1976). (cited in MPEP at §2164.08(c)). As recently clarified by the Court, an element is critical if its omission would result in the invention being wholly inoperative:

> [The dissent] cites *In re Mayhew* for the proposition that "claims failing to recite a necessary element of the invention fail for lack of an enabling disclosure." There, however, the method claims omitted a step without which the invention as claimed was wholly inoperative (meaning it simply would not work and could not produce the claimed product).

Amgen Inc. v Hoechst Marion Roussel Inc. 65 USPQ2d 1385, 1403 (CAFC 2003) (emphasis added).

The MPEP provides the following guidance in determining whether an element is critical:

> In determining whether an unclaimed feature is critical, the entire disclosure must be considered. Features which are merely preferred are not to be considered critical. *In re Goffe*, 542 F.2d 564, 567, 191 USPQ 429, 431 (CCPA 1976). Limiting an applicant to the preferred materials in the absence of limiting prior art

> would not serve the constitutional purpose of promoting the progress in the useful arts. Therefore, an enablement rejection based on the grounds that a disclosed critical limitation is missing from a claim should be made only when the language of the specification makes it clear that the limitation is critical for the invention to function as intended. Broad language in the disclosure, including the abstract, omitting an allegedly critical feature, tends to rebut the argument of criticality.

MPEP at §2164.08(c) (emphasis added).

In *In re Johnson and Farnham*, 194 USPQ 187, 196 (CCPA 1977), the Court overturned a rejection based on the grounds that a disclosed critical limitation was missing from the claims. The claims at issue were drawn to a chemical polymer. The specification taught that the invention required a minimum "sigma value" for one of the constituent subunits, but the minimum value was not recited in the claims. The examiner had rejected the claims for failing to recite the minimum value on the basis that this minimum value was a critical element of the invention, and the rejection had been upheld by the Board. However, the Court overturned the rejection, stating:

> The PTO would limit appellants to claims reciting a sigma value of at least 0.7. This view is improper because it requires the claims to set forth the practical limits of operation for the invention and it effectively ignores the scope of enablement provided by the specification as a whole.

In re Johnson and Farnham at 196. As stated by the Court, "it is the function of the specification, not the claims, to set forth the "practical limits of operation" of an invention" (citing *In re* Rainer, 134 USPQ 343, 346 (1962) and, further, "[o]ne does not look to claims to find out how to practice the invention they define, but to the specification." (citing *In re Roberts* 176 USPQ 313, 315 (CCPA 1973) and *In re Fuetterer*, 138 USPQ 217 (1963)).

Factual Evidence of Record

Applicants wish to draw to Examiner's attention art already of record that provides factual evidence that refutes that assertion that elements discussed in Example 4 are critical elements without which the invention would be wholly inoperative. Suni et al., 1998, J. Immunol. Methods. 221:89-98[2] is Applicants' first publication in a scientific

[2] Applicants also provided Examiner with a copy of Suni et al., 1998, J. Immunol. Methods. 221:89-98 during the interview on August 20, 2003.

journal of the methods of the present invention using whole blood samples. The teachings of Suni et al. are discussed below as they relate to the teachings of Example 4.

Example 4

The rejection was based on the teachings of Example 4, which Examiner suggested represent critical elements of the invention. Applicants submit that Example 4 describes a preferred mode of the invention and is not a teaching of critical limitations without which the invention would be wholly inoperative.

First, the specification describes the invention in broad terms omitting allegedly critical elements discussed in Example 4 (see, in particular, the description of the invention "at its simplest" at page 4, lines 11-15, and in claim 1 as filed). This broad language in the disclosure omitting the allegedly critical features tends to rebut the argument of criticality.

Secondly, the specification states that "The examples illustrate certain preferred embodiments of the invention but are not intended to be illustrative of all embodiments" (page 13, lines 16-17; see also page 18, lines 13-14) (emphasis added). This language in the specification further rebuts the argument of criticality.

Finally, Applicants discuss the specific language of Example 4 and show that Example 4 does not teach critical limitations without which the invention would be wholly inoperative. Example 4 describes four key areas in which the antigen-specific methods of the invention differ from the prior art methods for analyzing T cell cytokine response to polyclonal stimulators: (1) the geometry of the T cell/accessory cell interaction; (2) the timing of the addition of Brefeldin-A and the use of exogenous costimulation; (3) gating on CD69; and (4) the number of events collected[3]. These four points are discussed separately, below.

The geometry of the T cell/accessory cell interaction

Example 4 states that "[T]he geometry of the T cell/accessory cell interaction was critical for AG responses; maximal responses were observed in slant tubes...." (page 16,

[3] The last paragraph of Example 4 provides further guidance directed to a particular narrow embodiment of the invention. Applicants believe that is not relevant to the rejection.

lines 13-14). In addition to the broad teaching of the specification as a whole (discussed above) that tends to refute the allegation that this is a critical element, the factual evidence of record demonstrates that the invention is operable without the use of slant tubes. In particular, Suni et al. (cited above) describe the methods of the present invention carried out using culture tubes incubated upright (see §2.2), which demonstrates that the enablement of the invention is not limited to use of the slant tubes. Based on this evidence, Applicants submit this teaching in Example 4 clearly describes a preferred mode of the invention and is not a teaching of a critical feature without which the invention would be wholly inoperative.

The timing of the addition of Brefeldin-A and the use of exogenous costimulation

The timing of the addition of Brefeldin-A and the use of exogenous costimulation are described as maximizing the results (page 16, lines 16-18), not as critical elements without which the invention would not operate. Applicants submit that a teaching of a way to maximize results represents no more than a teaching of a preferred embodiment. Features which are merely preferred are not to be considered critical.

Gating on CD69

Gating on CD69 is described as enhancing the results (page 16, lines 18-20), not as a critical element without which invention would not operate. Applicants submit that a teaching of a way to enhance the results represents no more than a teaching of a preferred embodiment. Features which are merely preferred are not to be considered critical.

Furthermore, the factual evidence of record demonstrates that the invention is operable without the use of gating of CD69. Suni et al. describe methods of the present invention carried out wherein the desired cells are identified using a cytokine-specific antibody and a T cell subset-defining antibody (anti-CD8) other than CD69, which demonstrates that the enablement of the invention is not limited to the use of CD69 as the subset-defining antibody (see In §3.2 and Figure 2).

The number of events collected

Example 4 further describes that accurate assessment of the responses required the routine collection and analysis of at least 50,000 events per determination. Applicants submit this teaching, which relates to the accuracy of the method, not the basic operability, represents guidance as to the practical limits of operation. It is a function of the specification, not the claims, to set forth the "practical limits of operation" of an invention.

Applicants further point out that Example 3 of the specification describes analyses were carried out using only 48,000 events (page 15, lines 15-16). Additionally, the factual evidence of record demonstrates that the invention is operable with fewer events collected. Suni et al. describe methods of the invention carried out in which 40,00-50,000 events were collected, which demonstrates that the enablement of the invention is not limited to the collection of at least 50,000 events (see in §2.4).

In summary, Applicants submit that when properly considered in view of the specification as a whole, Example 4 does not teach critical elements without which the invention would be wholly inoperative. In fact, Example 4 teaches preferred embodiments of the invention and sets forth practical limits of operation. Features which are merely preferred are not to be considered critical, and it is a function of the specification, not the claims, to set forth the "practical limits of operation" of an invention. Furthermore, factual evidence of record refutes the assertion that the elements discussed in Example 4 are critical to the operation of the invention. For the reasons discussed above and in view of the cited case law, the rejection, based on the grounds that a disclosed critical limitation is missing from the claims, is without basis and should be withdrawn.

Applicants respectfully request reconsideration and withdrawal of the rejection of Claims 19-24, 26-55, and 61-63 under the enablement requirement of 35 U.S.C. §112, first paragraph.

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Conclusion

Applicants respectfully submit that all rejections have been traversed or rebutted and that the application is in condition for allowance. Applicants respectfully request that all pending claims be allowed.

Respectfully submitted,

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Date

Douglas A. Petry, Ph.D.
Reg. No. 35,321
Agent for Applicants
BD Biosciences
2350 Qume Drive
San Jose, CA 95131
Tel: (408) 518-5074
Fax: (408) 954-4122